

Amendments to the Drawings

The attached sheets of drawings include changes to Figure 2 and Figure 6. These sheets replace the original sheets including Figure 2 and Figure 6. In both Figure 2 and Figure 6, the corresponding SEQ ID NOs have been added.

Attachment: Replacement Sheets
Annotated Sheets Showing Changes

REMARKS

In the present amendment, claims 1, 5, 6, 16 and 29 have been amended. Claim 16 has been canceled. The amendments to the claims are supported throughout the specification, in the claims and in the sequence listing. In addition, the specification has been amended at page 10 to indicate that the patent or application file contains at least one drawing executed in color as required under 37 CFR § 1.84, and to correct a typographical error on page 46. No new matter is believed to be added.

After entry of these amendments, claims 1-3, 5-15, 17-27 and 29-39 are pending.

Drawings/Specification

The drawings stand objected to under 37 CFR § 1.83(a) because Figures 3 and 7 purportedly fail to show the colors as described in the Brief Description of the Figures. Applicants respectfully submit that the as-filed figures included two color figures: FIGS. 3 and 7. Submitted herewith is a Petition under 37 CFR § 1.84 requesting acceptance of these color drawings.

In addition, the specification stands objected to for referencing an attorney docket number. Applicants have removed this reference. Withdrawal of this objection is requested.

The specification also stands objected to for containing sequence disclosures that fail to comply with the requirements set forth in 37 CFR § 1.821. Applicants have amended the specification to include the corresponding SEQ ID NOs for the sequences on page 96. The Examiner also alleges that Tables I-V represent linear amino acid sequence disclosures, and, therefore, need a heading identifying the protein name and its corresponding SEQ ID NO.

Applicants have amended the specification accordingly although they respectfully point out that Table II does not correlate to a SEQ ID NO so only a descriptive title has been added.

Applicants have also amended claim 1 so that it recites SEQ ID NO:1 and points out that SEQ ID NO:1 and SEQ ID NO:13 are the same sequence. Additionally, Applicants have amended Figures 2 and 6 to include the proper corresponding SEQ ID NOs. Replacement drawings and Annotated drawings showing the changes are enclosed herein. Applicants have also amended the specification on page 10 to correct the corresponding SEQ ID NOs in the figure legend.

The Examiner has also objected to the specification for containing hyperlinks. Applicants have amended the specification to remove the hyperlinks on pages 22 and 96. Withdrawal of this objection is requested.

Rejection of claims 1 and 5 under 35 U.S.C. § 101

The Examiner has rejected claims 1 and 5 as allegedly being directed to non-statutory subject matter without requiring the performance of a result outside of a computer or representing some type of physical transformation which is concrete or tangible. That rejection is respectfully traversed to the extent the rejection is applied to the claims as amended.

Applicants have amended claims 1 and 5 to include the step of screening the chemical entity in an assay that characterizes binding to said GR Site II in order to comply with 35 U.S.C. § 101. Applicants respectfully request reconsideration by the Examiner and withdrawal of this rejection.

Rejection of claims under 35 U.S.C. § 112, second paragraph

Claims 1, 5-10, 16, 27 and 29 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. That rejection is respectfully traversed to the extent the rejection is applied to the claims as amended

(a) The Examiner alleges that the phrase “any part of the cavity” in claim 1, 6 and 29, and the phrase “any part of” in claim 5, renders the claims indefinite. Applicants have amended these phrases to read “the cavity” and “said GR Site II,” respectively. By this amendment, Applicants believe that they have obviated this rejection.

(b) The Examiner alleges that the amino acid residues in claims 1, 5, 6, 27 and 29 do not match the amino acid sequence of SEQ ID NO:13 as well as those in Figure 2. Applicants have amended the specification on page 10 and Figure 2 so that the SEQ ID NOs correspond accurately. Additionally, Applicants have amended claim 1 to refer to SEQ ID NO:1. Support for this amendment can be found throughout the specification, for example on page 96, lines 15-31. By this amendment, Applicants believe that they have obviated this rejection.

(c) The Examiner alleges that the phrase “human GR; rat GR...” in claim 16 renders the claim indefinite. Applicants have amended claim 16 to include the corresponding SEQ ID NOs

as defined in Figure 6. By this amendment, Applicants believe that they have obviated this rejection.

(d) The Examiner has rejected claims 7-10 under 35 U.S.C. § 112, second paragraph, as they are dependent upon rejected independent claims. As the independent claims have been amended to overcome the Examiner's rejections, Applicants believe that the rejection of claims 7-10 has been overcome as well.

Rejection of claims under 35 U.S.C. § 102(e) and § 103(a)

The Examiner has rejected claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 102(e) and § 103(a) as allegedly being anticipated by or, in the alternative, as obvious over US patent 6,965,850 (hereinafter "'850").

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)). Therefore, '850 must describe each and every element of claims 1, 5 and 6 in order to anticipate these claims under Section 102(b).

Applicants respectfully submit that '850 does not teach each and every element of the claims. Amended claims 1, 5, 6 and 29 are directed to methods for evaluating the potential of a chemical entity to bind to a GR Site II, methods of designing a ligand of a GR Site II, methods for identifying modulators of a GR, and methods of identifying a ligand of a GR Site II, respectively. Amended claims 1, 5, 6 and 29 also recite that the GR Site II is comprises the amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 and is defined by the structure coordinates according to Table 1. Amended claim 1 also recites the structure coordinates according to Tables, III-V.

In contrast to the instant invention, '850 describes the use of compounds binding to the co-activator binding site of NHRs which is not Site II. Site II of the instant invention is situated on almost the opposite side of the protein from the Site II that is disclosed in '850. In addition, Site II of the instant invention comprises a different amino acid sequence than that disclosed for the Site II disclosed in '805. Site II of '850 comprises amino acids V571, I572, A574, V575,

A578, K579, F584, Q592, M593, L596, Q597, W600, E751, M752, and E755-I757 which are different from Site II of the instant invention. Further, the structural coordinates disclosed in '850 are different than those recited in the instant claims. Because '850 teaches neither the Site II nor its structural coordinates recited in the instant claims, it does not teach every element of the claims 1, 5 and 6, as amended, or of dependent claims 7-10, 27 and 29, and, therefore, does not anticipate the instant claims. Thus, Applicants respectfully request reconsideration by the Examiner and withdrawal of this rejection.

Claims 1, 5-10, 16, 27 and 29 also stand rejected under §103(a) as being unpatentable over '850. As discussed above, Applicant submits that '850 does not disclose the subject matter of the claims 1, 5 and 6, as amended, nor claims 7-10, 27 and 29 that ultimately depend therefrom. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

The Examiner has also rejected claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 103(a) as being unpatentable over WO 00/52050 (hereinafter "'050") in view of US Patent 5,856,116 (hereinafter "'116").

Amended claims 1, 5 and 6 are directed to methods for evaluating the potential of a chemical entity to bind to GR Site II, wherein said GR Site II is a structure described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:1 according to Table I, Table III, Table IV or Table V. These structure coordinates are not disclosed in either '050 or '116. As such, Applicants submit that '050 does not disclose the subject matter of the claims 1, 5 and 6, as amended, nor claims 7-10, 27 and 29 that ultimately depend therefrom and, therefore, do not render these claim obvious. Applicants respectfully submit that '116 does not cure the deficiencies of '050, and that accordingly the combination of '050 and '116 does not suggest Applicants' claimed invention. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

The Examiner has also rejected claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 103(a) as being unpatentable over US Patent Application Publication No. 2005/0181362 (hereinafter "'362). Specifically, the Examiner alleges that '362 teaches the crystallization of the complex of GR ligand binding with two ligands and the determination of the three-dimensional structure by the X-ray diffraction method.

Amended claims 1, 5 and 6 are directed to methods for evaluating the potential of a chemical entity to bind to GR Site II, wherein said GR Site II is a structure described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:1 according to Table I, Table III, Table IV or Table V. These structure coordinates are not disclosed in '362. As such, Applicants submit that '362 does not disclose the subject matter of the claims 1, 5 and 6, as amended, nor claims 7-10, 27 and 29 that ultimately depend therefrom and, therefore, do not render these claim obvious. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

Rejection of claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 103(a) over '362 in view of '850

The Examiner has rejected claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 103(a) as being unpatentable over '362 in view of '850. For the foregoing reasons, '362 does not disclose the subject matter of the claims 1, 5 and 6, as amended, nor claims 7-10, 27 and 29 that ultimately depend therefrom and, therefore, do not render these claim obvious. Applicants respectfully submit that '850 does not cure the deficiencies of '362, and that accordingly the combination of '362 and '850 does not suggest Applicants' claimed invention. Applicants request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, allowance of the application is respectfully requested. The Examiner is invited to contact the undersigned if there are any questions concerning the prosecution of this application.

The Commissioner is authorized to charge Deposit Account 19-3880 (Bristol-Myers Squibb Company) for any requisite fees due or to credit any overpayment.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
609-252-4323

Melissa Handler
Melissa Handler, Ph.D.
Agent for Applicants
Reg. No. 52,988

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FIGURE 2 (continued)

RXAlpha	306	WNELLIASFS	HRSIAV.....	..KDGILLAT	GL...HVHRN ..S..AHSAG VG.....
RARgamma	267	CLDILMLRIC	TRY...TPE.	..QDTMTFSD	GL...TLNRT ..Q..MH... ..NAGF....
PR	755	WMSLMVFGLG	WRSYK....H	VSGQMLYFAP	DL...ILNEQ ..R..MKESS FY.....
AR	742	WMGLMVFAMG	WRSFT....N	VNSRMLYFAP	DL...VFNEY ..RM.HKSRM Y.....
ERalpha	382	WLEILMIGLV	WRSME.....	HPGKLLFAP	NL...LLDRN ..Q.GKCVEG MV.....
ERbeta	331	WMEVLMGGLM	WRSID.....	HPGKLIFAP	DL...VLDRD ..E.GKCVEG IL.....
VitDR	216	AIEVIMLRSN	ESF...TMD.	...DMSWTCG	N.QDYKYRVS ..D..VT... ..KAGH....
PPARgamma	322	VHEIIYTMLA	SLM...NK..	...DGVLISE	GQ...GFMTR E.F..LK... ..SLRK
MR	806	WMCLSSFALS	WRSYK....H	TNSQFLYFAP	DL...VFNEE ..KM..HQSAM YE.....
TRbeta	301	CMEIMSLRAA	VRY...DPE.	..SETLTLNG	EM...AVTRG ..Q..LK... ..NGGL....
GR	600	WMFLMAFALG	WRSYR....Q	SSANLLCFAP	DL...IINEQ ..R..MTLPC MY.....
RXAlpha	345	...A.IF.DR	VLTELVSKMR	DMQMDKTELG	CLRAIVL.FN PDSKG...LS
RARgamma	305	..GP.LT.DL	VFAFAGQLL.	PLEMDDTEIG	LLSAICL.IC GDRMD...LE
PR	796	...S.LC.LT	MWQIPQEFV.	KLQVSQEEFL	CMKVLLL.LN .TIP.LEGLR
AR	783	...S.QC.VR	MRHLSQEFG.	WLQITPQEFIL	CMKALLL.FS .IIP.VDGLK
ERalpha	422	...E.IF.DM	LLATSSRFR.	MMNLQGEEFV	CLKSIIILLNS .GV..... YTF.LSSTLK
ERbeta	371	...E.IF.DM	LLATTSRFR.	ELKLQHKEYL	CVKAMILLNS LVTAT.Q
VitDR	255	..SLELI.EP	LIKFQVGLK.	KLNLHEEEHV	LLMAICI.VS PDRPG...VQ
PPARgamma	359	PFGD.FM.EP	KFEFAVKFN.	ALELDDSDIA	IFIHAVII.LS GDRPG...LL
MR	848	...L..C.QG	MHQISLQFV.	RLQLTFEENY	IMKVLLL.LS .TIP.KDGLK
TRbeta	339	..GV.VS.DA	IFDLGMSLS.	SFNLDDEVA	LLOAVLL.MS SDRPG...LA
GR	641	...D..QCKH	MLYVSELH.	RLQVSYEEYL	CMKTLLL.LS .SVP.KDGLK
RXAlpha	386	...NPAEVEA	LREKVYASLE	AYCKH..KYP EQPG.....	...RFAKLLL RLPALRSIGL
RARgamma	336	...EPEKVDK	LQEPLLEALR	LYARR..RRP SQPY.....	...MFPRMLM KITDLRGIST
PR	837	...SQTOFEE	MRSSYIRELI	KAIG...LRQ K...GVV..S	SSQRFYQLTK LLNLHDLVK
AR	824	...NQKFFDE	LRMNYIKELD	RIIA...CKR K...NPT..S	CSRRFYQLTK LLDSVQPIAR
ERalpha	467	SLEEKDHIHR	VLDKITDTLI	HLMA...KAG L...TLQ..Q	QHERLAQLL ILSHIRHMSN
ERbeta	411	DADSSRKLAH	LLNAVTDALV	WVIA...KSG I...SSQ..Q	QSMRLANLLM LLSHVRHASN
VitDR	297	...DAALIEA	IQDRLSNTLQ	TYIRC..RHP PP.L.....	LYAKMIQ KLAIDLRLSNE
PPARgamma	402	...NVKPIED	IQDNLLQALE	LQLKL..NHP ESSQ.....	...LFAKLLQ KMTDLRQIVT
MR	888	...SQAAFEE	MRTNYIKELR	KMVT.KCPNN S...G...Q	SWQRFYQLTK LLDSMHDLV
TRbeta	380	...CVERIEK	YQDSFLLAFE	HYINY..RKH HVTH.....	FWPKLLM KVTDLRMIGA
GR	681	...SQELFDE	IRMTYIKELG	KAIV...KRE G...N..SSQ	NWQRFYQLTK LLDSMHEVVE
RXAlpha	432	KCLEHLFFFK	LIGDTPIDTF	LMEMLEAPHQ MT.....
RARgamma	382	KGAERA.....	ITLKMEI PGP...MPP LIREMLENP.
PR	886	QLHLYC.....L
AR	873	ELHQFT.....F
ERalpha	519	KGMEHL.....Y
ERbeta	463	KGMEHL.....L
VitDR	342	EHSKQY.....RCLSFQP ECSMK..LTP	LVLEVFG...
PPARgamma	448	EHVQLL.....QVIKKTET DMS...LHP	LLQEIYKDL.
MR	937	DLLEFC.....F
TRbeta	426	CHASRF.....LHMKVEC PT...ELFPP	LFLEVFE...
GR	730	NLLNYC.....F

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FIGURE 6

u87951 Squirrel
AF141371 Pig
113196 Guinea Pig
u87953 Marmoset
u87952 Ma'z Monkey
Human
m14053 rat
x04435 mouse

MDSKESLTP. GKEENPSSVL TQERGNVMDF CKILRGGATL KVSVSSTSLA
MDLKESVTSS . KEVPSSVL GSERRNVIDF YKTVRGGATV KVSVSSTSLA
MDSKESLTP. GKEENPSSVL TQERGNVMDF CKILRGGATL KVSVSSTSLA
MDSKESLTP. GKEENPSSVL TQERGNVMDF SKILRGGATL KVSVSSTSLA
MDSKESLTP. GREENPSSVL AQERGDVMDF YKTLRGGATV KVSVSSTSLA
MDSKESLAPP GRDEVPGSLL GQGRGGSVMDF YKSLRGGATV KVSVSSTSLA
MDSKESLAPP GRDEVPGSLL GRGRGGSVMDL YKTLRGGATV KVSVSSTSLA

u87951 Squirrel
AF141371 Pig
l13196 Guinea Pig
u87953 Marmoset
u87952 Ma'z Monkey
Human
m14053 rat
x04435 mouse

u87951 Squirrel
AF141371 Pig
113196 Guinea Pig
u87953 Marmoset
u87952 Ma'z Monkey
Human
m14053 rat
x04435 mouse

KAVSLSMGLY	MGETETKVMG	NDLGFPQQGQ	ISLSSGETDL	QLLEESIANL
KAVSLSMGLY	MGETETKVMG	SDLGFPQQGQ	ISLSSGETDF	RLLEESIANL
KAVSLSMGLY	MGETETKVMG	NDLGFPQQGQ	ISLPSGETDF	RLLEESIANL
KAVSLSMGLY	MGETETKVMG	NDLGFPQQGQ	ISLSSGETDL	QLLEESIANL
KAVSLSMGLY	MGETETKVMG	NDLGFPQQGQ	ISLSSGETDL	QLLEESIANL
KAVSLSMGLY	MGETETKVMG	NDLGFPQQGQ	ISLSSGETDL	QLLEESIANL
KAVSLSMGLY	MGETETKVMG	NDLGYPQQGQ	LGLSSGETDF	RLLEESIANL
KAVSLSMGLY	MGETETKVMG	NDLGYPQOGQ	LGLSSGETDF	RLLEESIANL

u87951 Squirrel
AF141371 Pig
113196 Guinea Pig
u87953 Marmoset
u87952 Ma'z Monkey
Human
m14053 rat
x04435 mouse

NRSTSVENP KSSASSSVSA APKEKEFPKT HSDVSSEQQN LKGQTGSNNG
SRSTSVENP KSSASAAGPA APAEKAFPKT HSDGAPEQPN VKGQTGTNGG
SRSTSVENP KNSASA.VSG TPTE.EFPKT QSDLSSSEQEN LKSQAGTNGG
NRSTSVENP KSSASSSVSA APKEKEFPKT HSDVSSEQQN LKGQTGTNGG
NRSTSVENP KSSASSSVSA APKEKEFPKT HSDVSSEQQN LKGQTGTNGG
NRSTSVENP KSSASTAVSA APTEKEFPKT HSDVSSEQQH LKGQTGTNGG
NRSTSVENP KSSTSATGCA TPTEKEFPKT HSDASSESEQQN RKSQGTGTNGG
NRSTSRPENP KSSTPAAGCA TPTEKEFPOT HSDPSSEEOON RKSOPGTNGG

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AF141371 Pig
113196 Guinea Pig
u87953 Marmoset
u87952 Ma'z Monkey
Human
m14053 rat
x04435 mouse

NVKLYTADQS TFDI....LQ DLEFSSGSPG KETNQSPWKS DLLIDENCLL
NVKLFDTDQS TFDIWRKKLQ DLELPSSGSPG KETSESPWSS DLLIDENCLL
NVK.FPPDQS TFDI....LK DLEFSSGSPG KERSESPWRP DLLMDESCLL
NAKLCTADQS TFDI....LQ DLEFSSGSPG KETNQSPWRS DLLIDENCLL
NVKLYTADQS TFDI....LQ DLEFSSGSPG KETNQSPWRS DLLIDENCLL
NVKLYTTDQS TFDI....LQ DLEFSSGSPG KETNESPWRs DLLIDENCLL
SVKLYPTDQS TFDL....LK DLEFSAGSPS KDTNESPWRs DLLIDEN.LL
SVKLYTTDQS TFDI....LQ DLEFSAGSPG KETNESPWRs DLLIDEN.LL

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FIGURE 2

RXRalpha	225	S.....ANEDM.....	PVE.RILEAE LAVE.PKTET
RARgamma	182	L.....SPQ..LEE..	LIT.KVSKAH QETF.P....
PR	682Q.....LI.	PLINLLMSIE ..PD.V....
AR	669C Q.....	P IFLNVLEAIE ..PG.V....
ERalpha	305SLALSLTAD	QMVSALLDAE ..PP.I....
ERbeta	261DALSPE	QLVLTLEAE ..PP.H....
VitDR	120	.LRPKL....SEE..QQR..	IIA.ILLDAH HKTY.D....
PPARgamma	207	E.....SAD..LRA..	LAK.HLYDSY IKSE.P....
MR	731S RA.....LT.	P SPVMVLENIE ..PE.I....
TRbeta	211KPEP TDE..EWE..	LIK.TVTEAH VATNAQ....
GR	523ATLPQLT.	P TLVSLLEVIE ..PE.V....
RXRalpha	249	YVEANMGLNP SSPNDPVTN.	IC.....
RARgamma	203	S LCQL.GKYTT N....
PR	699I YAGHDNTKPD	TSSLLTS..
AR	685V CAGHDNNQPD	SFAALLSS..
ERalpha	327L YSEYDPTRPF	SEASMMGL..
ERbeta	281V LISR.....	TEASMMMS..
VitDR	145	P
PPARgamma	TYSDFCQFR
MR	750V YAGYDSSKPD	TAENLLST..
TRbeta	236	G SHWKQKRKFL P....
GR	544L YAGYDSSVPD	STWRIMTT..
RXRalpha
RARgamma	214	..SSADHRVQ L.....
PR
AR
ERalpha
ERbeta
VitDR	155	PPVRV....NDGGGSVTL	ELS.....
PPARgamma	228LTKAKAR AILTGKTTDK	SPFVIYDMNS LMMGEDKIKF
MR
TRbeta	248	..EDIGQAPK V.....
GR
RXRalpha	271Q.....AADK	OLFTLVEWAK RIPHFSELPL DDQVILLRAG
RARgamma	223DLGLWDK FSE..	LATK CIIKIVEFAK RLPGFTGLSI ADQITLLKAA
PR	718LNQLGER	QLLSVVVKWSK SLPGFRNLHI DDQITLIQYS
AR	705LNELGER	QLVHVVWKWAK ALPGFRNLHV DDQMAVIQYS
ERalpha	345LTNLADR	ELVHMINWAK RVPGFVDLTL HDQVHLLECA
ERbeta	294LTKLADK	ELVHMISWAK KIPGFVELSL FDQVRLLESC
VitDR	172QLSMLPH LAD..	LVSY SIQKVIGFAK MIPGFRDLTS EDQIVLLKSS
PPARgamma	265	KHITPLQEQQ KEVAIRIFQG CQF..	RSVE AVQEITEYAK SIPGFVNLDL NDQVTLLKYG
MR	769LNRLAGK	QMIQVVKWAK VLPGFKNLPL EDQITLIQYS
TRbeta	257DLEAFSH FTK..	IITP AITRVVDFAK KLPMFCELPC EDQIILLKGC
GR	563LNMLGGR	QVIAAVVKWAK AIPGFRNLHL DDQMTLLQYS

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FIGURE 2 (continued)

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FIGURE 6 (Continued)

u87951 Squirrel
 AF141371 Pig
 113196 Guinea Pig
 u87953 Marmoset
 u87952 Ma'z Monkey
 Human
 m14053 rat
 x04435 mouse

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 AF141371 Pig
 113196 Guinea Pig
 u87953 Marmoset
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 m14053 rat
 x04435 mouse

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 u87953 Marmoset
 u87952 Ma'z Monkey
 Human
 m14053 rat
 x04435 mouse

u87951 Squirrel
 AF141371 Pig
 113196 Guinea Pig
 u87953 Marmoset
 u87952 Ma'z Monkey
 Human
 m14053 rat
 x04435 mouse

u87951 Squirrel
 AF141371 Pig
 113196 Guinea Pig
 u87953 Marmoset
 u87952 Ma'z Monkey
 Human
 m14053 rat
 x04435 mouse

SPLAGEEDSF LLEGNSNEDC KPLILPDTKP KIKDNGDLVL SSSNVTLpq
 SPLAGEEDPF LLEGSSTEDC KPLVL PDTKP KVKDNGELIL PSPNSVPLpq
 SPLAGEDDPF LLEGNSNEDC KPLILPDTKP KIKDNGDGIL SSSNSVPQpq
 SPLAGEEDSF LLEGNSNEDC KPLILPDTKP KIKDNGDLVL SSSNVTLpq
 SPLAGEEDSF LLEGNSNEDC KPLILPDTKP KIKDNGDLVL SSSNVTLpq
 SPLAGEDDSF LLEGNSNEDC KPLILPDTKP KIKDNGDLVL SSPSNVTLpq
 SPLAGEDDPF LLEGNTNEDC KPLILPDTKP KIKDTGDTIL SSPSSVALpq
 SPLAGEDDPF LLEGDVNEDC KPLILPDTKP KIQDTGDTIL SSPSSVALpq

VKTEKEDFIE LCTPGVIKQE KLSTVYCQAS FPGANIIGNK MSAISIHGVs
 VKTEKEDFIE LCTPGVIKQE KLGPAYCQAS FSGANIIGGK MSAISVHGVS
 VKIGKEDFIE LCTPGVIKQE KLGPVYCQAS FSGANIIGNK MSAISVHGVS
 VKTEKEDFIE LCTPGVIKQE KLSTVYCQAS FPGANIIGNK MSAISIHGVs
 VKTEKEDFIE LCTPGVIKQE KLSTVYCQAS FPGANVIGNK MSAISIHGVs
 VKTEKEDFIE LCTPGVIKQE KLGPVYCQAS FPGANIIGNK MSAISVHGVS
 VKTEKDDFIE LCTPGVIKQE KLGPVYCQAS FSGTNIIGNK MSAISVHGVS
 VKTEKDDFIE LCTPGVIKQE KLGPVYCQAS FSGTNIIGNK MSAISVHGVS

TSGGQMYHYD MNTA.SLSQQ QDQKPIFNVI PPIPGSENW NRCQGSGDDN
 TSGGQLYHYD MNTAASLSKQ QEQQPLFNVI PPIPGSENW NRCQGSGDDN
 TSGGQMYHYD MNTA.SLSQQ QDQKPIFNVI PPIPGSENW NRCQGSGEDN
 TSGGQMYHYD MNTA.SLSQQ QDQKPIFNVI PPIPGSENW NRCQGSGDDN
 TSGGQMYHYD MNTA.SLSQQ QDQKPIFNVI PPIPGSENW NRCQGSGDDN
 TSGGQMYHYD MNTA.SLSQQ QDQKPIFNVI PPIPGSENW NRCQGSGDDN
 TSGGQMYHYD MNTA.SLSQQ QDQKPVFNVI PPIPGSENW NRCQGSGEDS
 TSGGQMYHYD MNTA.SLSQQ QDQKPVFNVI PPIPGSENW NRCQGSGEDN

LTSLGTLNFP GRTVFSNGYS SPSMRPDVSS PPSSSSTATT GPPP KLCLVC
 LTSLGTLNFS GRSVFSNGYS SPGMRPDVSS PPSSSSAAT. GPPP KLCLVC
 LTSLGTVNFP GRSVFSNGYS SPGLRPDVSS PPSSSS.TT GPPP KLCLVC
 LTSLGTLNFP GRTVFSNGYS SPSMRPDVSS PPSSSSTATT GPPP KLCLVC
 LTSLGTLNFP GRTVFSNGYS SPSMRPDVSS PPSSSSTATT GPPP KLCLVC
 LTSLGTLNFP GRTVFSNGYS SPSMRPDVSS PPSSSSTATT GPPP KLCLVC
 LTSLGALNFP GRSVFSNGYS SPGMRPDVSS PPSSSSAAT. GPPP KLCLVC
 LTSLGAMNFA GRSVFSNGYS SPGMRPDVSS PPSSSSTAT. GPPP KLCLVC

SDEASGCHYG VLTCGSCKVF FKRAVEGQHN YLCAGRNDI IDKIRRKNCp
 SDEASGCHYG VLTCGSCKVF FKRAVEGQHN YLCAGRNDI IDKIRRKNCp
 SDELSGCHYG VLTCGSCKVF FKRAVEGQHN YLCAGRNDI IDKIRRENCP
 SDEASGCHYG VLTCGSCKVF FKRAVEGQHN YLCAGRNDI IDKIRRKNCp
 SDEASVCHYG VLTCGSCKVF FKRAVEGQHN YLCAGRNDI IDKIRRKNCp

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FIGURE 6 (Continued)

u87951 Squirrel	ACRYRKCLQA GMNLEARKTK KKIKGIQQAT TGVSQETSEN PANKTIVPAT
AF141371 Pig	ACRYRKCLQA GMNLEARKTK KKIKGIQQAT TGVSQETSEN SANKTIVPAT
113196 Guinea Pig	ACRYRKCLQA GMNLQARKTK KKIKGIQQAT TGVSQNTSEN P.NKTIVPAT
u87953 Marmoset	ACRYRKCLQA GMNLEARKTK KKIKGIQQAT TGVSQETSEN PANKTIVPAT
u87952 Ma'z Monkey	ACRYRKCLQA GMNLEARKTK KKIKGIQQAT TGVSQETSEN PANKTIVPAT
Human	ACRYRKCLQA GMNLEARKTK KKIKGIQQAT TGVSQETSEN PGNKTIVPAT
m14053 rat	ACRYRKCLQA GMNLEARKTK KKIKGIQQAT AGVSQDTSEN P.NKTIVPAA
x04435 mouse	ACRYRKCLQA GMNLEARKTK KKIKGIQQAT AGVSQDTSEN .ANKTIVPAA
u87951 Squirrel	525 LPQLTPTLVS LLE VIEPEVL YAGYDSTV PD STWRIMTTLN MLGGRQVIAA
AF141371 Pig	489 LPQLTPTLVS LLE VIEPEVL YAGYDSSIPD STWRIMTA LN MLGGRQVIAA
113196 Guinea Pig	519 LPQLTPTLVS LLE VIEPEVI HSGYDSTSPD STWRIMTTLN MLGGRQVIAA
u87953 Marmoset	525 LPQLTPTLVS LLE VIEPEVL YAGYDSTV PD STWRIMTTLN MLGGRQVIAA
u87952 Ma'z Monkey	525 LPQLTPTLVS LLE VIEPEVL YAGYDSSV PD STWRIMTTLN MLGGRQVIAA
Human	525 LPQLTPTLVS LLE VIEPEVL YAGYDSSV PD STWRIMTTLN MLGGRQVIAA
m14053 rat	543 LPQLTPTLVS LLE VIEPEVL YAGYDSSV PD SAWRIMTTLN MLGGRQVIAA
x04435 mouse	531 LPQLTPTLVS LLE VIEPEVL YAGYDSSV PD SAWRIMTTLN MLGGRQVIAA
u87951 Squirrel	575 VKWAKAIPGF RNLHLD DQMT LLQYSWMFLM AFALGWR SYR QASSNLLCFA
AF141371 Pig	539 VKWAKAIPGF RNLHLD DQMT LLQYSWMFLM VFALGWR SYR QSSASLLCFA
113196 Guinea Pig	569 VKWAKAIPGF KNLHLD DQMT LLQYSWMFLM AFALGWR SYK QSNGSLLCFA
u87953 Marmoset	575 VKWAKAIPGF RNLHLD DQMT LLQYSWMFLM AFALGWR SYR QASSNLLCFA
u87952 Ma'z Monkey	575 VKWAKAIPGF RNLHLD DQMT LLQYSWMFLM AFALGWR SYR QASSNLLCFA
Human	575 VKWAKAIPGF RNLHLD DQMT LLQYSWMFLM AFALGWR SYR QSSANLLCFA
m14053 rat	593 VKWAKAILGL RNLHLD DQMT LLQYSWMFLM AFALGWR SYR QSSGNLLCFA
x04435 mouse	581 VKWAKAIPGF RNLHLD DQMT LLQYSWMFLM AFALGWR SYR QASGNLLCFA
u87951 Squirrel	625 PDLIINEQRM TLP CMYDQCK HMLYVSSELH RLQVS YEEYL CMK T LLLSS
AF141371 Pig	589 PDLVINEQRM ALPCMYDQCR HMLYVSSELQ RLQVS YEEYL CMK T LLLSS
113196 Guinea Pig	619 PDLIINEQRM SLP WMDQCR YMLYVSSELK RLQVS YEEYL CMK T LLLSS
u87953 Marmoset	625 PDLIINEQRM TLP CMYDQCK HMLYVSSELH RLQVS YEEYL CMK T LLLSS
u87952 Ma'z Monkey	625 PDLIINEQRM TLP CMYDQCK HMLYVSSELH RLQVS YEEYL CMK T LLLSS
Human	625 PDLIINEQRM TLP CMYDQCK HMLYVSSELH RLQVS YEEYL CMK T LLLSS
m14053 rat	643 PDLIINEQRM SLP CMYDQCK HMLFVSSELQ RLQVS YEEYL CMK T LLLSS
x04435 mouse	631 PDLIINEQRM TLP CMYDQCK HMLFISTELQ RLQVS YEEYL CMK T LLLSS
u87951 Squirrel	VPKDGLKSQE LFDEIRMTYI KELGKAIVKR EGNSSQNWQR FYQLTKLLDS
AF141371 Pig	VPKDGLKSQE LFDEIRMTYI KELGKAIVKR EGNSSQNWQR FYQLTKLLDS
113196 Guinea Pig	VPKEGLKSQE LFDEIRMTYI KELGKAIVKR EGNSSQNWQR FYQLTKLLDS
u87953 Marmoset	VPKDGLKSQE LFDEIRMTYI KELGKAIVKR EGNSSQNWQR FYQLTKLLDS
u87952 Ma'z Monkey	VPKDGLKSQE LFDEIRMTYI KELGKAIVKR EGNSSQNWQR FYQLTKLLDS
Human	VPKEGLKSQE LFDEIRMTYI KELGKAIVKR EGNSSQNWQR FYQLTKLLDS
m14053 rat	VPKEGLKSQE LFDEIRMTYI KELGKAIVKR EGNSSQNWQR FYQLTKLLDS
x04435 mouse	VPKEGLKSQE LFDEIRMTYI KELGKAIVKR EGNSSQNWQR FYQLTKLLDS

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FIGURE 6 (Continued)

u87951 Squirrel
AF141371 Pig
113196 Guinea Pig
u87953 Marmoset
u87952 Ma'z Monkey
Human
m14053 rat
x04435 mouse

MHEVVENLLN YCFQTFLDKT MSIEFPEMLA EIITNQLPKY SNGNIKKLLF
MHDVVENLLN YCFQT.....
LHEIVGNLLN ICFKTFLDKT MNIEFPEMLA EIITNQLPKY SNGDIKKLLF
MHEVVENLLN YCFQTFLDKT MSIEFPEMLA EIITNQLPKY SNGNIRKLLF
MHEVVENLLN YCFQTFLDKT MSIEFPEMLA EIITNQLPKY SNGNIKKLLF
MHEVVENLLN YCFQTFLDKT MSIEFPEMLA EIITNQIPKY SNGNIKKLLF
MHEVVENLLT YCFQTFLDKT MSIEFPEMLA EIITNQIPKY SNGNIKKLLF
MHDVVENLLS YCFQTFLDKS MSIEFPEMLA EIITNQIPKY SNGNIKKLLF

u87951 Squirrel
AF141371 Pig
113196 Guinea Pig
u87953 Marmoset
u87952 Ma'z Monkey
Human
m14053 rat
x04435 mouse

HQK (SEQ ID NO:14)
... (SEQ ID NO:15)
HQK (SEQ ID NO:16)
HQK (SEQ ID NO:17)
HQK (SEQ ID NO:18)
HQK (SEQ ID NO:19)
HQK (SEQ ID NO:20)
HQK (SEQ ID NO:21)